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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,330	06/21/2005	Nathan Bryan Mantlo	X-15710	8686

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

NOTIFICATION DATE	DELIVERY MODE
09/13/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/540,330	MANTLO ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-44,46-48 and 50-58* is/are pending in the application.

4a) Of the above claim(s) *6,23,28 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8,11-18,20-22,24-26,30,32-34,44,46-48 and 50-57* is/are rejected.

7)☒ Claim(s) *5,7,9,10,19,27,29,31,35-37,39-43 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4-44, 46-48 & 50-58 are pending in the instant application; of which **Claims 5, 6, 23, 26-28, 30-32, 38 & 39** are withdrawn and **Claims 4, 8, 11, 13, 18-21, 36, 40 & 41** are currently amended. **Claims 1-3, 45, 49, 59 & 60** are canceled. Therefore, examination on the merits of **Claims 4, 7-22, 24, 25, 29, 33-37, 40-44, 46-48 & 50-58** is found herein.

Response to Amendment

Applicant's amendments, see Amendment – After Non-Final Rejection, filed 06/27/2007, with respect to **Claims 4, 8, 11, 13, 18-21, 36, 40 & 41** have been fully considered and are entered. The 102-prior art anticipatory rejection of **Claim 1** has been withdrawn per amendment; however, new rejections are made herein. The 103-prior art obviousness rejection of **Claim 1** is withdrawn per amendment.

Response to Arguments

Applicant's arguments filed 06/27/2007 have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). However, the 103-prior art obviousness rejection of **Claims 46-48 & 50-55** is withdrawn in view of a new 102-prior art anticipatory rejection made herein.

Rejoined Inventions

Claims 5, 26, 27, 30-32, 38 (in part: the last species wherein X = O) & 39 are directed to inventions that fall within the scope of the elected group. Therefore, said claims have been included in the search and examination. As pointed out herein (Claim Objections): **Claim 5** (**X** = O) is unnecessary in view of **Claim 4** and **Claim 38** (in part: the last species) is the same species as in **Claim 39**. Therefore, the Examiner suggests deleting the last species in **Claim 38** in view of **Claim 39** to avoid a future double patenting issue and leaving the remaining species of **Claim 38** withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

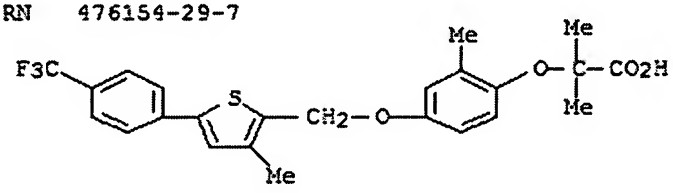
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

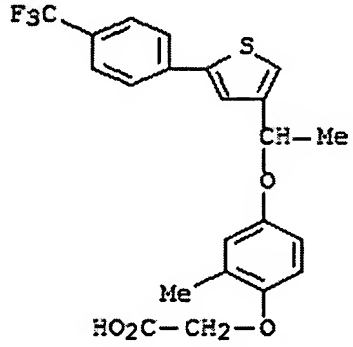
Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 4, 8, 11-18, 20-22, 24-26, 30, 32, 33, 44, 46-48, 50, 52, 56 & 57 are rejected under 35 U.S.C. 102(a & e) as being anticipated by Beswick *et al.* (*see* previous office action; WO 2002092590, published 11/21/**2002**, filed 05/09/2002; US Patent 7,091,237, published 8/15/**2006**). Said publications teach several species and a genus of trifluoromethyl-phenyl-thienyl-phenoxy acetic acids. Said compounds can be formulated into compositions and are useful in the treatment of PPAR-mediated diseases. Shown below are the anticipatory species:

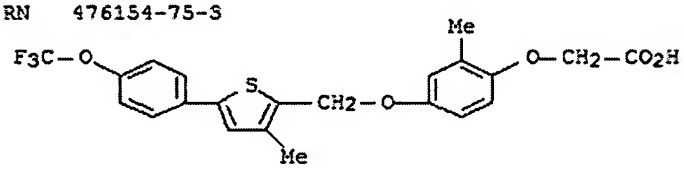
RN 476154-29-7



RN 476154-96-8



RN 476154-75-3



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beswick *et al.* (*see* previous office action; WO 2002092590, published 11/21/**2002**, filed 05/09/2002; US Patent 7,091,237, published 8/15/**2006**).

Determination of the scope and content of the prior art (MPEP § 2141.01)

Said publications teach several species and a genus of trifluoromethyl-phenyl-thienyl-phenoxy acetic acids. Said compounds can be formulated into compositions and are useful in the treatment of PPAR-mediated diseases. Shown above are the anticipatory species.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the anticipatory species cited above and the compounds of **Claim 34** is the position of X relative to Y. In the prior art the relative position is para and in **Claim 34** the position is meta.

Finding of prima facie obviousness--rational and motivation (MPEP § 2142-2413)

One skilled in the art would have found the claimed compounds prima facie obvious because it is well established that nothing unobvious is seen in substituting the known claimed isomers, as taught by Beswick *et al.*, since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. *In re Norris,* 84 USPQ 458 (**1950**).

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51 & 53-55 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions and a method of *treatment* of certain diseases mediated by PPAR, (such as diabetes and Metabolic Syndrome as it is defined on page 29 of the specification), does not reasonably provide enablement for preventing the progression of cardiovascular disease, treating demyelating disease, treating arthritis, or inflammatory diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***

6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art***

each of which is discussed in turn below.

The nature of the invention

The nature of the invention is compounds and compositions of Formula I and methods of using these compounds to treat PPAR related diseases.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case*, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for weight reduction, obesity, and type II diabetes, but it does not mean that the same

group of compounds and compositions may treat arthritis, demyelating diseases or inflammatory disease, nor further prevent the progression of cardiovascular disease.

In a recent publication by Bailey *et al.* (*Nature Immunology* **2005**, *6(10)*, 966-967), the authors cast doubt on the usefulness of PPAR ligands and their usefulness towards treating inflammation. Detailed throughout and specifically in the summary, the report points out that many issues remain unsolved. Answers to such issues are necessary to bring understanding to the scope of PPAR agonists in repressing inflammation.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the preventing the progression of cardiovascular disease or treating arthritis, demyelating diseases or inflammatory disease, as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of Formula I to treat clinical conditions of pertaining to glucose, cholesterol, and triglyceride levels, as well as PPAR binding, are found on pages 92-108.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claim 51 is drawn to method for the preventing the progression of cardiovascular disease. In order to prevent a progression of a disease, one would need to precisely

demonstrate that the identified subject did continue having the disease, and that such an effect was the direct result of administration of the claimed invention. In other words, the method may treat the disease and even prevent symptoms thereof, but the underlying disease is still within the patient. To "prevent the progression" of the disease is equivalent to eliminating the disease altogether within the patient.

Claims 53-55 are drawn to the treatment of arthritis, demyelating diseases or inflammatory disease. Such claims are not supported within the instant disclosure. Further, inflammatory disease is of a wide scope, (as compared to inflammation), and includes diseases such as COPD and Crohn's Disease, which are not treatable via the PPAR receptors.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Examiner suggests deleting "or preventing the progression of" in **Claim 51** and canceling **Claims 53-55**.

Claim Objections

Claim 4 is objected to because of the following informalities: under the subsection (a) there are two commas in a row (second line) and an unnecessary "and" after "alkyl," and before "wherein". Likewise in subsection (g) there is an unnecessary "and" after "A," and before "wherein", etc.

Claim 5 (withdrawn) is objected to for not further limiting and should be canceled.

Claim 10 is objected to because of the following informalities: there should be a space between "Claim" and "7".

Claim 12 is objected to because of the following informalities: there should be a space between "Claim" and "11".

Claims 21 & 22 are objected to because of the following informalities: there is an unnecessary comma between "R3" and "and R4".

Claims 30 & 32 are objected to because of the following informalities: the structures are not clear as to whether the phenyl group (containing R10 & R11) is in a fixed position or a variable position.

Claim 36 is objected to as being a duplicate to Claim 11 and should be canceled.

Claim 37 is objected to because of the following informalities: it is dependent on Claim 6, which is withdrawn; and should be withdrawn as well.

Claim 39 is objected to because of the following informalities: the word "acid" should be inserted after the word "acetic".

Claim 56 is objected to because of the following informalities: there should be a space between "Claim 53" and "wherein".

Claim 57 is objected to because of the following informalities: the claim fails to further limit the compound as defined by Claim 11. Examiner suggests canceling.

Claims 19, 27, 29, 31, 39, 40-43 & 58 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Appropriate correction is required.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

REBECCA ANDERSON
PATENT EXAMINER

for Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: September 6, 2007